vide useful information regarding age of onset or type or severity of clinical symptoms.

The testing of children is also controversial. There is concern that asymptomatic children with known genetic mutations may be raised "differently" (so-called self-ful-filling prophecy). Most centers delay DNA testing of children until they reach adulthood and can make the testing decision for themselves. An exception to this rule would be the testing of children who have symptoms of the disease and would benefit from an accurate diagnosis.

Many genetic disorders may be caused by different mutations at the same site on a chromosome. A DNA test for only a specific mutation may therefore be negative, even though the patient clinically has signs of the disease. The most vivid example of this is Duchenne type muscular dystrophy, in which there are over 50 different genetic variants of abnormalities in the dystrophin gene that all phenotypically present as Duchenne's; as many as 30% of these patients have a negative DNA test. DNA testing in prenatal diagnosis is also complex and involves many of the same legal and ethical issues that surround abortion.

It is difficult for the busy clinician to know which genetic tests are commercially available. A website exists to provide up-to-date information on the availability of both commercial and research genetic tests (http://healthlinks.washington.edu/helix). Another website, http://www.ncbi.nlm.nih.gov, has clinical information regarding the Human Genome Project and an online version of Victor McKusick's textbook, *Mendolian Inheritance in Man*; it is frequently updated as new information about genetic disorders is published.

DNA testing for neurogenetic diseases is a powerful and valuable diagnostic tool that should be used judiciously on an individual basis. The decision to proceed with such testing should be made only after considering all of the potential risks and benefits.

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Issues for Women with Epilepsy

EPILEPSY IS A NEUROLOGICAL DISORDER affecting 1% or more of the population. While the incidence of epilepsy is not significantly different between men and women, epilepsy raises special concerns and challenges for women. Female physiology alters the expression of seizures and may influence medication efficacy. Seizures and antiepileptic drugs (AEDs) alter hormones of the hypothalamus, pituitary, and gonads and may affect reproduction. Pregnant women with epilepsy risk more frequent seizures, pregnancy complications, and AED-related birth defects.

Many hormones influence brain electrical excitability, including gonadal and adrenal steroids and thyroid hormone. Estrogen has a seizure activating affect in experimental models and in humans, whereas progesterone has a seizure-protective effect. These neuroactive steroids alter the synthesis of the inhibitory neurotransmitter GABA and of the $GABA_A$ receptor, and they also alter activity at membrane receptors for GABA and for the excitatory neurotransmitter, glutamate. Approximately 30% of women with epilepsy report catamenial (menstrual associated) seizure patterns, with seizures more likely to occur in the perimenstrual period. Little information is available regarding changes in epilepsy at menopause or with postmenopausal hormone replacement therapy.

AEDs that alter the hepatic cytochrome P450 (cyP450) enzyme system are associated with changes in the metabolism and protein-binding of endogenous and contraceptive steroid hormones. Medications that induce cyP450 enzymes and reduce steroid hormone concentrations include phenytoin, carbamazepine, barbiturates, and topiramate. Women on these AEDs experience a failure of oral hormonal contraceptives of 6% or more per year. The risk is highest with hormonal contraceptives containing low doses of estrogen (35 µg or less). The failure risk at higher hormone doses (50 µg of estrogen) is not known, although the risk theoretically should be less. Drugs that inhibit or have no effect on the cyP450 enzyme system do not compromise hormonal contraception. Felbamate and valproate inhibit the cyP450 enzymes and gabapentin; lamotrigine and vigabatrin have no effect. For women on cyP450-inducing AEDs, barrier methods of contraception should be considered.

Reproductive function may be adversely impacted in women with epilepsy. Fertility rates in women with epilepsy are one-third those of nonepileptic siblings. Women with epilepsy have a higher frequency of anovulatory menstrual cycles, abnormal menstrual cycle length, and polycystic ovaries than do nonepileptic women. Reproductive endocrine disorders described in women with epilepsy include abnormalities in basal and pulsatile luteinizing hormone secretion, elevations in pituitary prolactin, and disturbances in gonadal steroids. These alterations in reproductive hormones occur both in women treated and in women not treated with AEDs. Until the mechanisms of reproductive dysfunction in women with epilepsy are delineated, symptomatic women should be referred for gynecologic evaluation.

Women with epilepsy are also at risk for sexual dysfunction. More than one-third of women with epilepsy experience disorders of sexual arousal. These manifest clinically as complaints of dyspareunia, vaginismus, and arousal insufficiency. Sexual desire may also be adversely affected. There are several etiologies to account for the sexual dysfunction in epilepsy. Seizures can restrict opportunities for forming and maintaining intimate relationships. Epileptic discharges can disrupt the function of brain structures mediating sexual behavior, such as the limbic cortex, and can disturb hypothal-

amic and pituitary hormone release. AEDs change levels of pituitary and gonadal hormones involved in sexual behavior by altering metabolism and protein binding and probably also through direct effects on the hypothalamic-pituitary axis. Women with sexual dysfunction should undergo an endocrine evaluation (thyroid hormones, estrogen, testosterone, and prolactin), psychological evaluation, and referral to a gynecologist. Changing to another AED is sometimes helpful.

Pregnancy raises several concerns for woman with epilepsy, including the risk of more frequent maternal seizures, of pregnancy complications, and of birth defects. Fortunately, a better understanding of the risks associated with pregnancy in the epileptic patient has led to treatment strategies to optimize outcome.

About 25% to 30% of women with epilepsy have more frequent seizures during pregnancy, while a similar number find that seizures are less frequent. Poor seizure control may be related to lower total levels of AED. To a lesser extent, the non–protein bound fraction of AED may be decreased as well. Women with epilepsy also have more pregnancy complications such as vaginal bleeding and abruptio placentae, and there is a two-fold increase in the incidence of adverse pregnancy outcomes, including fetal wastage and neonatal and perinatal death.

AED use during pregnancy is associated with a higher risk of fetal malformation. The risk of congenital malformation, such as cleft lip or palate and ventricular septal defect, is 4% to 8% in infants of mothers with epilepsy who are exposed to any AED, compared to 2% to 4% of infants born to women without epilepsy. There is a 1% to 2% incidence of neural tube defects in fetuses exposed to valproic acid during the first trimester, and a 0.5% to 1% risk after exposure to carbamazepine. Congenital anomalies, mostly involving the mid-face and digits, occur in between 5% to 30% of infants exposed to AEDs. AED-associated teratogenesis may occur because of fetal exposure to toxic free-radical AED intermediates. Particularly susceptible people are those with deficiencies in free-radical metabolizing enzymes. Malformations may also occur as a result of AED-related folate deficiency.

Specific treatment strategies can significantly reduce these risks. Treatment with folate before conception and during pregnancy substantially reduces the risk of neural tube defects in nonepileptic women who are at risk and is thought to confer the same protective action in women with epilepsy. The optimal dose is not established but appears to be between 0.4 mg and 4 mg per day. Indicated prenatal diagnostic testing for women with epilepsy includes high resolution ultrasound and maternal serum alpha-fetoprotein obtained between 16 and 18 weeks gestation; neural tube defects will be detected with greater than 95% sensitivity. Vitamin K is administered during the final month of pregnancy as oral Vitamin K1 (phytonadione, 10 mg per day) to prevent AED-associated fetal and maternal coagulopathy. Adverse outcomes are minimized by treating with AED monotherapy, rather than polythera-

py, and by using the lowest effective AED dose. Monitoring the non–protein bound fraction of AED is most accurate during gestation.

The new AEDS (felbamate, gabapentin, lamotrigine, tiagabine, topiramate) have limited human pregnancy experience, but these drugs have not been teratogenic in animals. A prospective AED pregnancy registry has been established by an independent scientific advisory group and financed by five pharmaceutical companies manufacturing AEDs. Women who become pregnant while receiving any AED should be encouraged to enroll with the registry (contact information is provided below).

Epilepsy is a chronic illness that affects women during the child-bearing years. The expression of epilepsy may be altered with physiological changes in ovarian steroid hormones and as a consequence of exposure to therapeutic steroid hormones. Fertility may be reduced because of alterations in the hypothalamic pituitary-gonadal axis, in gonadal steroid concentrations, and in ovarian morphology. Sexual dysfunction may present as specific physiological complaints. Pregnancy and fetal outcome can be maximized by maintaining seizure control, utilizing AED monotherapy, and reducing peak-dose exposure. Routine folic acid supplementation appears prudent for any woman of child-bearing potential on AEDs. Further information is available for health care professionals and consumers through the Epilepsy Foundation.

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New Pharmacological and Surgical Therapies for Parkinson's Disease

REPLACEMENT THERAPY WITH dopamine precursors (levodopa) or dopamine agonists remains the mainstay of symptomatic therapy for Parkinson's disease. Two new selective dopamine D-2 and D-3 receptor agonists, pramipexole and ropinirole, are now available. Both are